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Comments to FDA Guidance for Industry – Drug Substance- Chemistry, Manufacturing, and Controls Information, Draft Guidance-January 2004 – Docket No. 2003D-0571

Dear Sirs and Madams,

We are pleased to provide comments on the recently issued Guidance for Industry.

The manufacture of APIs is subject to the requirements of GMP defined in the ICH Harmonized Tripartite Guideline: Good Manufacturing Practice for Active Pharmaceutical Ingredients. The regulatory bodies of the European Union, Japan, and the USA have adopted this guideline.
Manufacture includes all operations of receipt of materials, production, packaging, storage, quality control, and release.
APIs can be manufactured by various methods. The CMC section in an application should represent the commitment for a determined manufacture of a drug substance. The documentation provided should comprise all information necessary to describe the current routine manufacture unambiguously. The documentation should not give information, which is subjected to the requirements of GMP.

Based on these principles we will make the following comments:

Lines 383 - 384
Building numbers or other specific identifying information should be deleted. *(GMP relevant)*

Line 409
Delete: The entire manufacturing process should be depicted.
The flow diagram should show the building of the final molecular structure beginning with the starting materials, which are identical with the GMP starting material. The entire manufacturing process should be part of the description of the manufacturing process. The flow diagram should not comprise any process know how and should be open to the applicants which do not manufacture the drug substance.

Lines 414 - 417 delete

Line 425 delete auxiliary materials

Line 426 delete

Line 427 delete

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Lines 428 - 430 delete

Line 431 delete

Line 449
Replace detailed description by narrative description.
Detailed is a too indefinitive word. The manufacturing steps should be described unambiguously but not detailed. Detailed descriptions are part of GMP.

Lines 457 - 458 Replace all process controls by critical process controls.
Only critical process controls should be highlighted, other process controls should be part of GMP or can be useful for other reasons (economic efficiency).

Lines 521 - 522 see comments lines 457 - 458
Only critical process controls should be included in the description.

Lines 600 - 618 Reworking
Reworking is considered a non-routine event like reprocessing. In practical operation, reworking occurs more infrequently than reprocessing. Therefore there should be no need for a prior approval supplement. Reworking should be handled like reprocessing. The internal requirements of the manufacturer should be different.

Lines 633 - 636 delete *(GMP relevant)*

Lines 640 - 643 delete *(GMP relevant: validation !)*

Lines 647 - 648
The material regeneration operations are GMP relevant and should not be described.

Lines 655 - 664 Other Operations
Recovery of drug substance from drug products or purification of aged material should be reworking, but only GMP relevant.

Lines 775 - 777
Noncritical parameters and tests should not be listed. *(GMP relevant)*

Lines 779 - 780
Justification of ranges, limits, or acceptance criteria is part of the validation, which is GMP relevant.

Lines 785 - 787
Critical process control values from relevant batches should not be provided.
This is part of the validation, which is GMP relevant.

Lines 868 - 888
Validation of sterilisation processes should be handled like the validation of other processes. Validation information should not be submitted.

Lines 890 - 910 Manufacturing Process Development
This chapter should be relevant only for new chemical entities and not for established drug substances e.g. used in generic drug products.

Lines 1021 - 1022 delete

Lines 1059 - 1062 delete
GMP relevant; can be reviewed during facility audits.

Attachment 1
Starting Materials for Synthetic Drug Substances

Lines 1676 - 1678
Change sentence 2:
The description of the manufacturing process in an application begins with the starting material or materials after which appropriate GMPs, as defined in ICH Q7a, applies.
ICH Q7a has been adopted by the FDA. Compliance with this guideline ensures the quality of a drug substance. In case of a need of information on the synthesis of a starting material, this information should be provided in the documentation to the starting material (e.g. the quality of the starting material is critical).

Lines1683 - 1685 delete the sentence
A drug substance is an appropriate starting material. It is one of the best-characterised starting materials, and reference can be made to master files or pharmacopoeias (see also the definition of starting materials in ICH Q7a).

Lines 1696 - 1708 Starting Materials with/without a Significant Nonpharmaceutical Market
The differentiation of the markets and/or manufacturers is not a good instrument to define quality criteria for API starting materials. Perhaps this is a new definition for articles of commerce.
The quality of the starting materials must be suitable to manufacture safe drug substances with a validated process. Selection principles should be identical for all starting materials.

Line 1743
Delete the restriction: that result in isolated and purified intermediates
Many modern and automated processes can run without isolation and/or purification of the intermediates. Often isolated intermediates are immediately further processed without testing.

Line 1753 Delete the sentence.
A purification step is often as important as the reaction step and should be counted equivalent to a reaction step.

Lines 1764 - 1766
Delete: or the extraction work up of a reaction mixture
Extraction can be an excellent method to isolate and purify products.

Lines 1775 - 1797 Carryover of Impurities
This selection principle should be deleted or modified.
The impurity profile of a drug substance must be acceptable independent of the origin of the impurities. Carryover of impurities should be avoided in each step of the synthesis beginning with the starting material. The proposal to define a chemical earlier in the manufacturing process (line 1737) if it is inconsistent with the starting material carryover criterion means that the impurity profile of the drug substance is unchanged but the impurities have new names.

Lines 1871 - 1893 delete *(see comment lines 1696 - 1708)*

Lines 1895 - 1971 Justification
The chapter justification should be rewritten based on the comments made before.
a) Propinquity
Flow diagram of the synthesis of the staring material
b) Carryover of Impurities
delete

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Attachment 2
Starting Materials of Plant or Animal Origin

Line 2009 delete nonpharmaceutical

Yours sincerely
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Quality Management